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Pharmacological Correction of the Human Functional State in High Altitude Conditions

by Mahnovsky V. P.

International University of Kyrgyzstan
255 Chui Prospect, Rm. #105,
Bishkek 720001,
Kyrgyz Republic

Summary: The effect of *Bemithylum* on metabolic changes of glucose, lactate, pyruvate, inorganic phosphate, uric acid, cholesterol, bilirubin, urea and creatinine in human blood during short-term residences in high mountain regions of Tien Shan and Pamir was investigated. To evaluate effectiveness of *bemithylum* for correction of metabolism, physical and mental workability of military personnel during short-term residence at 2800m altitude the subjects were tested by 2,5-kilometer marsh with fast temp in mountain canyon as a maximal physical exercise and by psychophysiological test "The Disarranged Lines" which were carried out before (as control exercise) and after pharmacological procedures. The subjects were separated to two groups: for first one (n = 7) was prescribed to take *bemithylum* in the dose of 750 mg per day by one or two 5-day treatments during initial period of high altitude adaptation, for second one (n = 8) was prescribed to take *placebo* in the same dose and period of the prescription. All the metabolic indicators mentioned above (excepting lactate and pyruvate) were measured spectrophotometricaly in the dried acid extracts of blood samples with standard monotests. It was shown that *bemithylum* makes essential psychoenergizing and stimulating effects on the processes of concentration and mental workability in conditions of high altitude hypoxia for the sake of direct influence on hemoprotein catabolism, i.e. preventing increase in bilirubin formation to the levels promoting its penetration through blood-brain. Excessive increase of blood cholesterol during physical exercises causes negative influence on human organism and significantly decreases his workability at 2800m altitude. *Bemithylum* prevents significant cholesterol accumulation in blood and simultaneously increases human physical workcapacity in conditions of high altitudes. In persons treated with pharmacological correction with *bemithylum*, time of making maximal physical exercise decreased more than by twice in comparison with the data received in subjects with *placebo*-effect. To approve action of *bemithylum* on increase of human hypoxic resistance and on prompting human adaptation and widening its limits in conditions of high mountain hypoxia was studied character of metabolic adaptation of persons with low hypoxic resistance with treatment of two 5-day correction procedures during 30-day residence at 3600 m altitude. The first 5-day procedure with *bemithylum* significantly decreased lactic acid accumulation (for 72.3%, P<0.01) and value of excess lactate (for 76.9%, P<0.01) in blood of subjects (n = 10) in comparison with group of low resistant persons who took *placebo* (n = 10). Increase of creatinine, cholesterol, uric acid and especially urea was also lowered for 22.5% (P<0.01), 27.1% (P<0.01), 59.8% (P<0.01) and 122.1% (P<0.01) in these persons accordingly. Further after two 5-day procedures this actoprotector reduced increase of glucose for 17.6%, lactic acid for 33.8%, uric acid for 19.3%, creatinie for 21.2%, urea for 179.3% and cholesterol for 74.3% in comparison with subjects with *placebo*-effect. The scheme of one 5-day treatment with *bemithylum* seems to be the most effective both for reducing of terms in achieving urgent adaptation to acute phase of high altitude hypoxia and for transfer of passive form of adaptation into active one. It is necessary to increase treatment with *bemithylum* to two 5-day procedures with obligatory one-day interval between procedures to rise adaptability and resistance of human organism to long-term residence in high altitude conditions.

Key words: High Altitude Hypoxia, Bimethylum, Exersise, Workability, Glucose, Bilirubin, Cholesterol, Adaptation

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INTRODUCTION

The problem to rise adaptive potential to the input of extreme environmental factors, to provide for optimal workability of a healthy human in taxing conditions of activities, attracts careful attention of many scientists and medical researchers both in our country and abroad in connection with practical importance and demands of military medicine and human applied physiology. Our previous studies [V.P.Mahnovsky et al., 1985a; V.P.Mahnovsky and R.V.Bolshedvorov, 1986] showed that preliminary individual selection of military personnel with low hypoxic resistance and their further dismissed from military service in high mountains (with transfer for serve in other conditions) allowed to decrease by 18% the number of illness among military personnel a serving at frontier posts in high mountains conditions. Also, the number of disadaptive disorders' cases among selected personnel decreased from 70-75 to 35 cases per year, practically there were no mortal cases from acute mountain sickness. However, there are still some cases of illness connected with disadaptive disorders among selected personnel with average (to 5%) and high (to 3%) hypoxic resistance, and particularly with low hypoxic resistance (10%), who were sent to serve on high mountains posts.

So, for more effectiveness to disclose and prevent disadaptive disorders we have to develop in parallel both the methods of diagnostic control of functional systems of human organism in conditions of high altitude adaptation and schemes of correctional procedures.

At present two main ways have been developed to rise a human hypoxic resistance. First, application of high mountain or pressure chamber training. Second, one includes use of pharmacological remedies and various biologically active substances which allow to reorganize quickly metabolism in conditions of oxygen deficiency.

In implementation of this prophylactic method the knowledge of biochemical mechanisms of adaptation is of great importance. Here the prospective way of biochemical prophylactics is believed to be the regulation of the processes of organism resistance rising with the help of natural protective compounds of close or equal to endogenic substances, participating in support of constant internal condition of organism. In a certain extent this is achieved with the help of natural protective endogenic substances (vitamins, neuromediators, hormones, antioxidants, etc.) or compounds with similar specter of activity which have regulative impact on different metabolic processes both on cellar and system levels, take part in the process of homeostasis and are capable to rise protective and adaptive opportunities of organism. With this it is necessary to take in mind that, first, it is necessary to have remedies (for pharmacological correction of hypoxia of different genesis) which selectively gave impact onto different chains of complicated mechanism of oxygen supplies, i.e. onto: (1) support of functions of respiratory system; (2) correction of functions of cardiovascular system; (3) effectiveness of organism transport system functioning (rheologic functions of blood, erythrocyte functions); (4) tissues energetic metabolism; and (5) functions of cellular and mitochondrial membranes [P.P.Denisenko, 1984].

The second, during period of hypoxic damage of different genesis and intensiveness in all organs and tissues without any exclusions there occur changes affecting realization of its functions. But the main changes are the changes in energetics, in keeping membrane structure and enzymatic ensembles unchanged, and in energy-related transformation of metabolic ways, so correction of these processes and states with pharmacological agents, capable targetly to interfere into these processes, is the most prospective direction of pharmacological correction of adaptation [A.S.Losev et al., 1986].

The third, pharmacological correction of hypoxic states is possible mainly on compensatory stage of hypoxia. It can be made both with substances recovering the flow of revitalizing equivalents through NAD-dependable part of the respiratory chain, and substances capable to shunt the electron flow in the same point [L.D.Lukyanova, 1984]. And it is necessary to take into account here that maximal protective effect of antihypoxic remedies occurs in organisms which are non-resistance to hypoxia, and that it is minimal for high resistant ones [L.D.Lukyanova, 1988; G.N.Chernobaeva, V.E.Romanova, 1988].

The most prospective compounds, having exposed antihypoxic abilities, are actoprotectors, whose activity more often combines with adaptogenic and anabolic effects of the

metabolic regulation remedies [A.S.Losev, 1991]. *Bemithylum*, membrano-active antioxidant has very important value among the compounds of this class.

Bemithylum (2-benzilidazol-thioethyl) is an original actoprotector which was obtained in the Research Institute of Pharmacology of the Russian Academy of Medical Sciences (Moscow) and is permitted for wide clinical use to rise human physical and mental workability in the taxing conditions by the State Pharmacological Committee of the Russian Federation. *Bemithylum* exposes positive effects with one-time treatment in the dose of 500-700 mg. By its pharmacological specter *bemithylum* makes some psychostimulating, antiastenic and adaptogenic effects, rises organism resistance to functional hypoxia and overheating, increases and rehabilitates organism workability during physical exercises.

Mechanism of *bemithylum* effect is connected with promoting cellular energoplastic supplies, gluconeogenesis activation and lactate utilization, increase of anabolic processes by means of direct influence RNA synthesis in cells and more economic oxygen utilization [A.V.Smirnov et al., 1990; S.A. Kryzhanovski et al, 1994]. Increase of RNA synthesis reactions is connected with the ability of *bemithylum* and its similar substances to interact with genom of different cells, which is explained by structural equality of benzilidazol derivatives and purines of nucleic acids [A.V.Smirnov et al., 1988]. Membrano-stabilizing and antioxidant effects was exposed in the specter of mechanism of *bemithylum* effect. It was proved that *bemithylum* is an active immunostimulator both on cellular and humoral levels. Possibly, it is specific and obligatory characteristic of all actoprotectors class. This compound also has exposed antimutagenic effect.

By the experiments with animals it was shown that *bemithylum* is capable to increase their physical workability, to make an ‘economizing’ effect on energetic metabolism which provides increase of cellular ATP concentration and lactate utilization [G.V.Morozov et al., 1987]. Smirnov A.V. [1991] showed that it decreases effects of motor hypoxia in animals during physical exercises by means of decreasing level of lactate in tissues and blood, and decreasing use of energetic resources.

Interesting data was received during study of *bemithylum* effect onto development of adaptive processes in animals and humans in conditions of pressure chamber hypoxia. So, with experiments on animals it was shown that use of this compound during 3-day impulse hypoxic training in pressure chamber increased the development of cross adaptation to physical exercises [A.V.Smirnov et al., 1991]. During these experiments the authors saw additional increase of endurance of the animals, improvement of biochemical indicators' values and increase of antioxidant enzymatic activity. A.Z. Zurdinov [1998], examining concentration of metabolites in animal blood after injections of *bemithylum* in normal conditions during 10 days and in combination with pressure chamber training at the "altitude" of 6,500 m, showed that after injection of the remedy there was mentioned the development of the new, more economic level of metabolic supplies of adaptive processes.

Clinical evaluation of *bemithylum* effectiveness, made during experiments with healthy volunteers in climatic pressure chamber showed that this actoprotector (in the dose of 500 mg) increases coefficient of oxygen utilization and level of aerobic-anaerobic switch [L.I.Voronin et al., 1988]. According to A.V. Smirnov et al. [1990], under dosed physical exercise it increased effectiveness of external breathing for 25-30% and decreased the increase of lactate in blood for 30%, and moderated subjective symptoms of mountain sickness. A.S. Shanazarov et al. [1988, 1999] studied *bemithylum* effect on antioxidative activity of superoxidedismutase (SOD) and some products of lipid peroxidation (LP) in blood serum of healthy young people placed at the altitude of 2100 m in Tien Shan mountains. It was shown that by mean of normalization of SOD activity the actoprotector prevents significant increase of malondialdehyde (an intermediate product of LP) in erythrocyte membranes and thereby it prevents cellular destruction.

The object of the present research was to study effect of *Bemithylum* on human metabolic changes in acute period of adaptation in high mountain regions of Tien Shan and Pamir. The goals were: (1) to evaluate effectiveness of *bemithylum* for correction of physical and mental workability of military personnel during short-term residence at 2800m altitude, (2) to approve action of this actoprotector on increase of human hypoxic resistance and on

prompting human adaptation and widening its limits in conditions of high mountain hypoxia (at 3600 m altitude).

METHODS

Subjects, protocol and data treatment: two seria of researches were conducted in mountain conditions:

- The first series: the purpose was to study *bemithylum* effect on military personnel capacity for work in process of high altitude adaptation. It included a study of the actoprotector influence both metabolism and mental workability of 15 normal males (with age of 18-20 years old) in the real conditions of military service activity in the first 10-day period of their residence at altitude of 2800 m over sea level (Tien Shan) and their endurance of maximal physical exercise. The subjects were separated to two groups: for first one (in the number of 7 persons) was prescribed to take the actoprotector in the dose of 750 mg per day during five days, for second one (in the number of 8 persons) was prescribed to take *placebo* in the same dose and period of the prescription.

Maximal physical exercise: 2,5-kilometer distance marsh with fast temp in mountain canyon. This marsh was carried out with the two groups of subjects in two times: before (as control exercise) and after the treatment of the pharmacological procedures.

Mental workability: for evaluation of concentration processes of the subjects was used a well-known psychophysiological test *"The Disarranged Lines"*, on the basis of results of which were calculated a time of solving the tasks and a number of mistaken solutions.

Indicators: an individual time of the distance overcoming by the subjects was measured. The some physiological (heart rate and arterial blood pressure) and biochemical (glucose - *Gl*, inorganic phosphate - Ph_i, cholesterol - *Ch*, bilirubin - *Br*, urea - *Ur*, creatinine - *Cr*) indicators' levels of these subjects were measured in blood samples before the pharmacological treatment and the maximal physical exercises - as control values, and after these ones. A rate of concentration change of metabolic indicators in blood was calculated.

- The second series included to study *bemithylum* effect on metabolism of 20 males with low hypoxic resistance (with age of 18-20 years old) in the real conditions of military service activity. This research was carried out in middle mountain conditions (at altitude of 1700 m over sea level) and then at 3600 m over sea level (Pamir): on 3, 7, 15 and 25 days of their adaptation. These subjects were separated to two groups: for 1st group (in the number of 10 persons) was prescribed to take *bemithylum* in the dose of 750 mg per a day by two 5-day treatments (with one-day break) during first eleven days of residence at 3600 m, for 2nd group (in the number of 10 persons) was prescribed to take *placebo* in the same dose and period of the prescription.

Indicators: glucose, lactic acid (lactate), pyruvic acid (pyruvate), uric acid (*U.A.*), cholesterol, urea and creatinine levels of these subjects were measured in blood samples before and after first- and second five-day treatments of *bemithylum* and *placebo* at altitude of 3600 m. The biochemical data of these subjects received in the middle mountains were used as control.

Selection procedure of the subjects with low hypoxic resistance was preliminary conducted on the basis of results of the dosed Flack test by our method [V.P. Mahnovsky, 1991]. These persons were there selected from majority of healthy military contingent located at altitude of 1700 m.

Data treatment: (1) for evaluation of character of hemodynamic changes the heart rate and arterial blood pressure (AP) were measured with the portable monitor of pulse and AP (made in Hungary); (2) for evaluation of character of changes of indicators of carbohydrate, lipid and nitrous metabolism in mountain conditions we used standard methods of spectrophotometric analysis. All the metabolic indicators mentioned above (excepting lactate and pyruvate) were measured in the dried acid extracts of blood samples with standard monotests of firm "Baker Instruments Limited" (USA) and firm "Boohringer Mannheim" (Germany) by centrifugal analyser "Centrifichem-600" (Baker Instruments Limited, USA). Calculation of these indicators was made in the relative units. Concentrations of lactate and pyruvate were measured in arterial blood simples accordingly W.E. Huckabee [1957]. On the

basis of these indicators there were calculated a ratio of lactate to pyruvate (*K*) and an excess of lactate (*ExL*) accordingly the following formulas:

$$K = L_i / P_i$$

K - coefficient of ratio of lactate concentration to pyruvate concentration, L_i - lactate concentration, P_i - pyruvate concentration

$$ExL = (L_e - L_c) - ((P_e - P_c) \times L_c \times P_c)$$

ExL - excess lactate (in relative units), L_c and L_e - concentrations of lactate before and after exercise, P_c and P_e - concentrations of pyruvate before and after exercise accordingly.

Statistical analysis of experimental data: Analysis of experimental physiological and biochemical data was made by parametrical statistics methods (T- and F-criteria) with standard programmes: "Biostatistics-2" and "Biostatistics-3" on personal computer "Apple". Coefficients of correlation between parameters were calculated depending on special research goals. For mathematical estimation of character and forces of correlation of these biochemical indicators and antihypoxic effect of *bemithylum* on metabolic system, human resistance and physical capacity in high altitude conditions a method of correlation analysis (with arranging the values of links between indicators and constructing correlation structures) was used.

RESULTS AND DISCUSSION

In table 1 means of the metabolic indicators are shown before and after maximal physical exercise in the acute period of adaptation to the altitude of 2800m taking into account of factor of *bemithylum* effect.

As our observation showed during the first day of residence at this altitude a significant increase of glucose level in blood for 11.5% ($P<0.01$) in all examined persons after control maximal physical exercise was registered. It is known that glucose level in blood during physical exercises may rise, decrease or stay the same as in rest condition. In working muscles a consumption of glucose increases and glycogen decay, glycolysis and lactic acid genesis are intensified as well, the lactic acid being as a substance of gluconeogenesis may stimulate glucose produce in lever [E. Newsholm and K. Stark, 1977].

At the same time it was found that bilirubin and especially cholesterol concentrations in blood increased accordingly for 9.9% ($P<0.05$) and 84.6% ($P<0.01$). Seems it shown that level of total cholesterol (and triglycerides) in blood plasma often correlates negatively with the level of physical activity [P.D. Wood et al., 1985; A. C. Arutzenius et al., 1985], sharp increase of this metabolite may certify significant decrease of physical tolerance in examined persons and their work capability in the initial period of high mountain acclimatization.

Changes in the other metabolic indicators concentrations (i.e. inorganic phosphate, urea and creatinine) in blood after making control maximal physical exercise in the first day of residence at the altitude of 2800m appeared to be statistically non-significant ($P>0.05$). Nevertheless, application of method of correlation structures for the analysis of the biochemical data of this physical exercise allowed to define general features and effect of the concentration level of these indicators on the process of biochemical adaptation and human resistance formation to the combined effect of maximal physical exercise and acute high altitude hypoxia.

So, in scheme 1 we see that the majority of the metabolic indicators after maximal physical exercise has significant correlation both with glucose level (*Ph_i:* $r = 0.698$; *Cr:* $r = 0.811$) and with rate of its concentration change in blood (*Cr:* $r = 0.761$). Simultaneously, significant correlation between individual time of the distance overcoming by the subjects (T) and rate of glucose concentration change ($r = -0.515$), showing that increase of glucose exchange rate in blood results to significant decrease in individual time making maximum physical exercise in conditions of high altitude hypoxia. Discovered interconnection of these indicators may be explained on the basis of the following data in literature.

It is well known that even in conditions of normal barometric pressure beginning from the first minutes of physical exercise the blood glucose plays important role as energetic

substrate for the oxidative process in muscles, because local amounts of carbohydrate there significantly decrease [J. Wahren et al., 1971]. During maximal physical exercises an ATP consumption for muscle contraction is so bigger that rate of substrate and oxygen supplies by blood is inadequate. Utilizations of blood glucose and muscle glycogen as prompt mobilizing energetic resources for muscle work increase sharply in these conditions. Thereby adrenaline secretion increases, that stimulates both producing glucose from glycogen in lever and splitting the glycogen to lactate [N.N.Yakovlev, 1974; A.L. Lehniger, 1982].

Time of adaptation	Phase of research		Glucose	Inorganic phosphate	Urea	Creatinine	Bilirubin	Cholesterol
Day 1	Control	Rest	6,95 (1,66)*	0,821 (0,188)	2,14 (0,67)	0,157 (0,002)	1,31 (1,00)	0,039 (0,002)
		Excercise	7,75 (3,56)	0,819 (0,048)	1,79 (0,82)	0,153 (0,003)	1,44 (2,06)	0,072 (0,018)
		P	<0,01	>0,01	>0,5	>0,5	<0,05	<0,01
Day 6	Bemithylum	Rest	8,35 (9,55)	0,720 (0,012)	1,86 (0,29)	0,172 (0,003)	1,75 (0,83)	0,048 (0,0015)
		Excercise	9,87 (3,58)	0,850 (0,25)	3,07 (1,93)	0,226 (0,016)	1,73 (1,93)	0,109 (0,0035)
		P	>0,05	<0,001	<0,01	<0,01	>0,05	>0,05
	Placebo	Rest	5,03 (0,66)	0,497 (0,004)	2,29 (2,1)	0,108 (0,0007)	0,68 (0,02)	0,023 (0,0002)
		Excercise	8,3 (8,58)	0,819 (0,09)	2,33 (0,3)	0,162 (0,001)	1,01 (0,09)	0,059 (0,0018)
		P	<0,001	<0,001	<0,01	<0,01	<0,01	<0,01

* dispersion

Table 1. Effect of *bemithylum* on metabolic indicators in acute period of subjects adaptation to the altitude of 2800m.

At the same time blood lactate, some amino acids and glycerol are converted by gluconeogenesis into glucose which then is transfered by blood to muscles and using both in recovery of glycogen reserves and in liquidation of oxygen debt. Another way on supplies of maximal ATP amount of skeleton muscles in critical circumstances is a splitting of creatine phosphate, - a high energetic compound which is a reserving donor of high energetic phosphate groups in filling uncoupled end-phosphate groups of ATP during muscle contractions. The creatine phosphate supplies exhaust promptly in working muscles and as result of it - ATP reduction, AMP disamination, rising concentration of ADP, Ph_i and creatinine where the latter is end-product of creatine phosphate split are observed [J.B. Dossetor, 1966; L. Stryer, 1981].

It is necessary to say that availability of significant correlation ($r = 0.667$) between inorganic phosphate level in blood after the physical exercise and concentration of blood urea, which is end-product of oxidative splitting of amino acids in lever and muscle tissues, seemly means drawing urea cycle into process of oxygen debt compensation during development of tissue hypoxia. Take into consideration a character of distribution ("architecture") of the correlation structures for these biochemical indicators we suppose as a working hypothesis that glucose-alanine cycle is one of important bioenergetic mechanisms supporting homeostasis during combined action of physical exercise and high altitude, so as it includes mobilization of blood glucose and increasing of its metabolic exchange between blood and tissues, and its interconnection with metabolites of other cycles, in particular with urea cycle. This cycle supplies working muscles of glucose from lever where for its produce is used carbon structure of alanine and transfers aminogroups to lever from skeleton muscles where the ones are converted into urea [A.L. Lehniger, 1982].

Summarizing results mentioned above we can conclude that combined effect of maximal physical exercises and high altitude hypoxia causes interconnective activation of the above showed bioenergetic metabolic cycles in human organism which is directed both to

liquidation of energetic debt in muscle and other tissues, and to metabolic formation of human adaptive resistance and his physical tolerance.

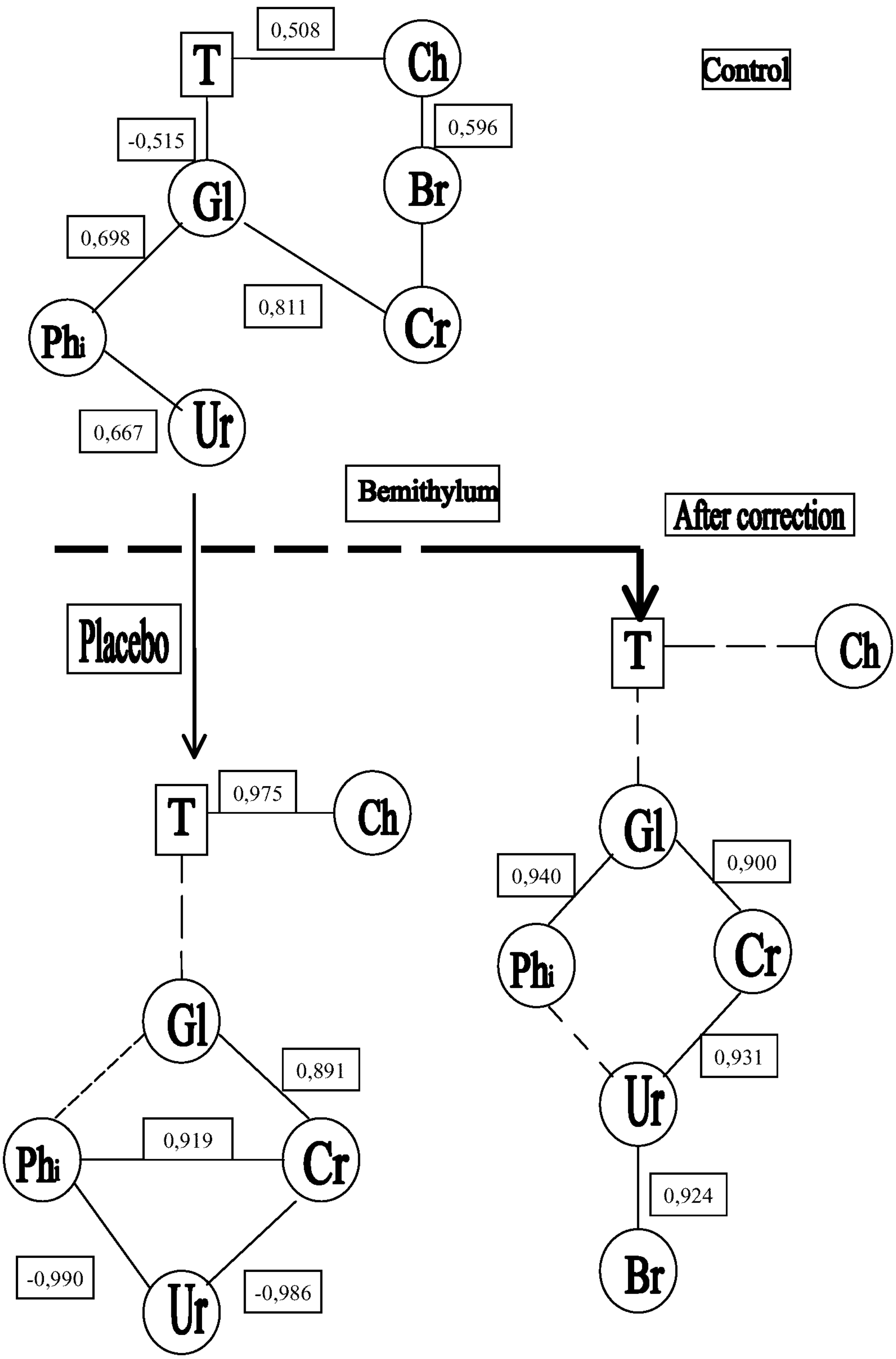
As scheme 1 shows correlation structure has continuation. So creatinine level correlates both with bilirubin level after physical exercise (r = 0.688) and with rate of its concentration change in blood (r = 0.599). In one's turn rate of bilirubun exchange correlates with rate value of cholesterol concentration change in blood (r = 0.596) that reflects equal-directed increase of bilirubin and cholesterol circulations between tissues and blood during control maximal physical exercise. Thereby, value of cholesterol increase in blood has significant positive correlation with individual time of the distance overcoming by the subjects (r = 0.508) which means that increase of time on making physical exercises is caused by essential rise of cholesterol concentration in blood. According to observations of a number of scientists a cholesterol produce increases both in mountain conditions and during physical activities [R.K. McDonald and V.C. Kelly, 1947; R. Bason and Ch.E. Billings, 1969; R. Silvester et al., 1977; A.R.P. Walker et al., 1982]. However, excessive increase of cholesterol concentration in blood under action of stress environmental factors are regarded by these authors as one of signs of functional tension of nonspecific adaptive mechanisms that causes decreased physical workability.

Use of 5-day procedure with *bimethylum* in acute period of high altitude adaptation caused significant effect on metabolic indicators' changes (Table 1). So persons who took *bimethylum* had lesser increase in blood levels of glucose, inorganic phosphate and creatinine in comparison with the data registered in the group of subjects who took *placebo*. These subjects had increase of mentioned indicators for 46.8%, 45.9% and 18.6% accordingly. Our results compared with the results of studies of *bemithylum* effect on energetic metabolism of S.S. Boiko et al. [1987] and G.V. Morozov et al. [1987] who found reducing consumption of creatine phosphate and lesser accumulation of lactic acid during physical exercises as result of this compound action.

The *bemithylum* caused also marked effect onto metabolic exchanges of cholesterol and bilirubin. Concentration of cholesterol and bilirubin significantly increased on the 6th day of mountain adaptation of subjects who took *placebo* (for 156.5% and 48.5% accordingly, $P<0.01$). At the same time persons taken *bemithylum* have non-significant changes in concentrations of these indicators before and after physical exercise.

Thereby, separate elements (links: *Gl–Cr* and *Ph$_i$–Ur*) in "architecture" of glucose-depending links of subjects taken *placebo* have maintained as in control research. However specific character of these correlations' forces and polarity is different (see scheme 1). So, correlative forces between rate of inorganic phosphate concentration change in blood and urea level registered after physical exercise significantly increased, and initial polarity of this connection changed (r = –0.990). The initial correlative forces between rate of glucose concentration change in blood and individual time of the distance overcoming by the subjects is significantly decreased (r = –0.053). New strong links have formed between creatinine increase and urea level in blood after physical exercise (r = –0.986), and also between creatinine level and inorganic phosphate (r = –0.919). Nevertheless, the change of polarity in link between inorganic phosphate and urea can indicate on essential changes in work of bioenergetic cycles.

At the same time, direct correlation between blood cholesterol increase and individual time of the distance overcoming increased approximately by two times in this group (r = 0.975). It corroborates once more that excessive rise of blood cholesterol influences negatively to human organism and reduces his workability during physical exercises in conditions of acute period of adaptation to high altitude hypoxia.



Scheme 1. Correlation structures of metabolic indicators in control and post-period of pharmacological correction after maximal physical exercises at altitude of 2800 m over sear level.

Analysis of correlation structures of biochemical indicators showed that "architecture" of glucose-depending links of subjects taken *bemithylum* is similar to the one of control research. But forces of correlation between indicators essentially increased in comparison to control and formed new significant interconnections as follows: *Cr–Ur* (r = 0.931) and *Ur–Br* (r = 0.924); there occure brake of links *Cr–Br* and *Ch–Br*. And correlation between blood cholesterol and individual time of the distance overcoming is statistically non-significant (r = 0.496). It is necessary to mention that glucose increase in blood in these persons during physical exercise was really decreasing in comparison with the data of control physical exercise, which is caused by economizing of glucose produce and also more effective use of glucose substrate by muscle tissues, so that glucose metabolic exchange between blood and tissues increased by 1.5 times ($P<0.01$).

Increase of glucose metabolic exchange rate between blood and tissues during physical exercise in comparison with the control data also occurs in group of subjects with *placebo*-effect. If we take into account that cellular oxygen utilization is directly proportional to the intensity of accumulated substrate transfer through membranes [H.Yost, 1975] we may state that these changes reflect sharply increased need of cells in energetic substrates in conditions of acute oxygen deficiency, connected with high energetic consumption of working muscles when oxygen utilization rate is increased.

Essential increase of correlative dependence between glucose and other metabolic indicators, and statistically significant lesser increase of their level after physical exercise confirm overall economizing and antioxidative (in case of bilirubin) effect of *bimethylum* on metabolic processes. When comparing these results with corresponding antihypoxic and rehabilitative effects of *bimethylum* we see that in conditions of combined effects of hypoxia and physical exercises at 2800m altitude the activity of this compound connected with decrease of energetic resources consumption, particularly with economizing glucose produce and its more effective use by muscle tissues. *Bemithylum* blocks substantial accumulation of blood cholesterol and thereby increases human physical fitness for work in high altitudes.

Table 2 shows that time of the distance (T) covered by the subjects who took *bemithylum* decreased more than by two times in comparison with the data received in group with *placebo*-effect. Besides, increase (Δ) of heart rate and systolic blood pressure decreased in these persons by 1.85 and 2 times accordingly. According to S.A.Kryzhanovsky et al. [1994] it can be explained that overall target of this actoprotector is optimization of activity of all organism physiological systems and decrease of physiological "value" of work unit.

Group	Time of adaptation	Phase of research		Heart rate (beats/ min) Mean±S.E.	Systolic pressure (mm of Hg) Mean±S.E.	ΔT (sec)
	Day 1	Control	Rest	82,2±4,42	120±5,17	
			Exercise	118,5±3,31	126±3,1	
			P	<0,05	>0,5	
I	Day 6	Bemithylum	Rest	81,0±60,07	116,3±2,63	79,2
			Exercise	101,7±5,0	128,6±4,46	
			P	>0,5	>0,5	
	Day 1	Control	Rest	74,0±2,06	111,7±4,01	
			Exercise	108±3,27	125,2±2,58	
			P	<0,05	<0,05	
II	Day 6	Placebo	Rest	64,0±5,19	108,3±2,47	162
			Exercise	109,0±5,23	134,2±1,54	
			P	<0,05	<0,05	

Table 2. The hemodynamic indicators and difference between meantime (ΔT) of the marsh distance overcoming by the 1st and 2nd groups before and after pharmacological correction at the altitude of 2,800m.

It is necessary to specially emphasize the inhibitory effect of *bemithylum* on excessive bilirubin accumulation, whose increased concentration can be examined as combined effect of high altitude and physical exercises to the level of hemogroups disintegration in hemoglobin [V.P.Mahnovsky et al., 1988].

Data of special literature shows that unconjugated bilirubin has pro-oxidative properties, and with excessive concentrations is capable to penetrate through blood-brain barrier [M.Perlman and J.W.Frank, 1988], to bound with tissues and damage cellular structures, especially CNS cells [S.T.Nilsen et al., 1984; T.W.R.Hansen and D.Bratlid, 1986]. There was established direct correlation between decrease of brain mitochondrial enzymatic activity (NADH cytochrome-c-reductase, ATP-ase) and accumulation of total and unconjugated bilirubin in the blood serum [V.A.S.Almeida and L.Rezende, 1981]. It is well known that bilirubin can be bounded with human erythrocyte membrane structures [F.A.Oski and J.L.Naiman, 1963; D.Bratlid, 1972; H.Sato and S.Kashiwamata, 1983], making bilirubin-erythrocyte complexes whose formation is a criteria sign of bilirubin encephalopathy origin risk [N.A.Kaufman at al., 1967; D.Bratlid, 1972]. It appears that bilirubin toxicity is accompanied by its direct relation with certain proteins or certain components of mitochondrial membranes.

It is necessary to emphasize that bilirubin is a product of hemoglobin hemogroup disintegration, whose main site binds with serum albumin and then transferred to lever. Human albumin has paramount high bounding site for bilirubin and also one or several low bounding sites [J.Jacobsen and R.P.Wennberg, 1974; K.S.Lee et al., 1975; N.P.Shabalov, 1982]. When direct (paramount) bounding site of albumin is saturated then prompt increase of unconjugated bilirubin amount in plasma occurs [R.Brodersen, 1980]. This is toxic bilirubin which is capable to interact with membranes of nervous cells, erythrocytes and to decrease activity of some membrane-bounded enzymes as a result of complex combination with phospholipids [R.Brodersen, 1979, 1980; S.Kashiwamata et al., 1981]. If we take into account that acute hypoxia significantly hinders bilirubin clearance from blood [J.Shorey et al., 1969] then its possibility to react with quite big number of cellular compounds significantly increases. This leads to aggravation of compensation process of hypoxic stress in organism, to decrease of his total resistance and adaptability, to changes in processes connected with consentration and thinking that are both supported by our previous research results [A.S.Shanazarov, V.P.Mahnovsky et al., 1989] and by data given in this paper.

In particular, in the first day of residence at 2800m altitude significant correlation between a number of mistaken solutions according to test of "Disarranged lines " and bilirubin level in blood (r = 0.900) in group with *placebo*-effect was founded. It continued to be the same and on the 6th day of mountain research (r = 0.833). Time of solving the tasks and a number of mistaken solutions were lesser in group of subjects with *bemithylum*-effect for 26.5% and 22% accordingly in comparison with control data, and the correlation between a number of mistaken solutions and bilirubin level was non-significant. The exposed protective effect of *bemithylum* on mental workability during climatic pressure chamber experiences was founded by other researchers. It was shown that use of this actoprotector in the dose of 500 mg decreased a number of mistakes in compensatory tracking and in addition of numbers in the regime of time deficit [L.I. Voronin et al., 1988]. In the conditions of pressure chamber hypoxia ("altitude" of 4500 m) *bemithylum* increased mental workability for 10% according to the re-encoding test [A.V. Smirnov et al., 1990]. It seems here the effectiveness of this compound is caused by its drooping psychostimulating and antiasthenic actions, and also by its possibility to accumulate selectively in cerebral structures, making psychoenergizing effect on cerebral metabolism [S.S. Boiko et al., 1987a] and neutralizing toxic effect of bilirubin.

Thus, application of 5-day procedure of *bemithylum* correction in acute period of adaptation to high altitudes makes activating influence on human physical and mental workability through restructuring of activity of metabolic cycles to economizing regime and providing more economic use of energetic substrates (glucose in particular) by tissues, as well as preventing excessive formation of cholesterol and bilirubin, and preserving sufficiently normal level of concentration.

Interesting data on *bemithylum* prescription to correct hypoxic resistance of military personnel and increase of their high altitude adaptability were received by us in the initial period of their residence at 3600m altitude in Pamir region.

Treatment of two 5-day procedures with *bemithylum* correction for persons with low hypoxic resistance allowed mainly to influence the process of their high altitude metabolic adaptation. So, already after one 5-day procedure with *bemithylum* significantly decreases lactic acid accumulation (for 72.3%, P<0.01), (Fig.1) and value of excess lactate (for 76.9%, P<0.01), (Fig.2) in blood in comparison with group of low resistant persons who took *placebo*. Increase of creatinine, cholesterol, uric acid and especially urea was also lowered for 22.5% (P<0.01), 27.1% (P<0.01), 59.8% (P<0.01) and 122.1% (P<0.01) in these persons accordingly (Fig.1).

At the same time essential increase of glucose in blood (for 45-55% in average) was observed in all subjects in groups with *placebo*- and *bemithylum*-effect , which can be explained by metabolic adaptation character of low resistant individuals in severe climatic conditions of Pamir. Nevertheless, further after two 5-day procedures with *bemithylum* (15th day of research) even in so called high altitude "desert" with specific climatic conditions of this region (i.e. with combination of hypoxia and very low humidity, high solar radiation and extremely poor range of colours of environment), this actoprotector made more economizing effect on concentration of above mentioned metabolites in blood, having reduced increase of glucose for 17.6%, lactic acid for 33.8%, uric acid for 19.3%, creatinie for 21.2%, urea for 179.3% and cholesterol for 74.3% in comparison with subjects with *placebo*-effect (Fig. 1).

As seen from Fig.1 and 2, on 25th day of adaptation to 3600m altitude recovering changes of the majority of these metabolic indicators occured in persons with *bemithylum*-effect. At the same time in persons with *placebo*-effect "excess" amount of lactate as well as concentration of uric acid, creatinine and especially glucose in blood appeared to be significantly increased (P<0.01) in comparison with group with *bemithylum*-effect.

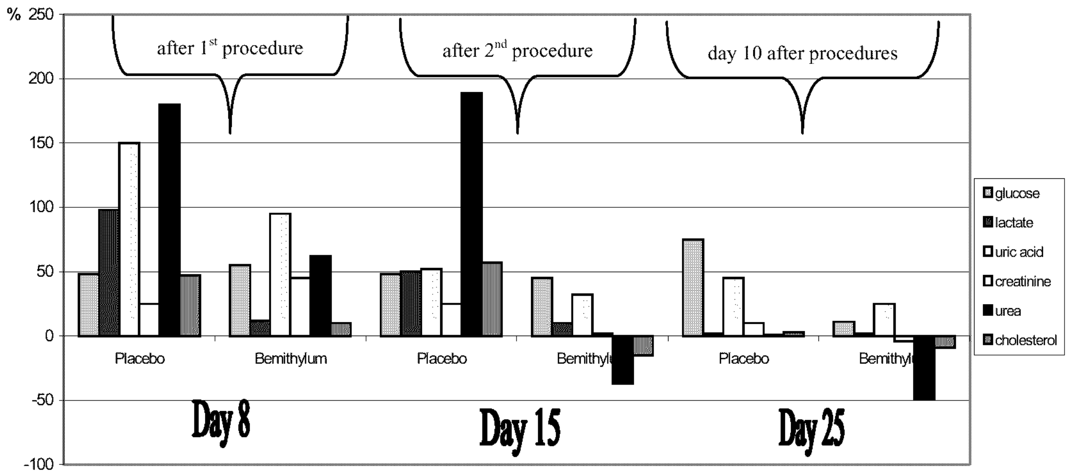


Figure 1. Effect of one and two 5-day procedures with bemithylum and placebo on metabolites' changes in blood of subjects with low hypoxic resistance during adaptation at 3600m altitude.

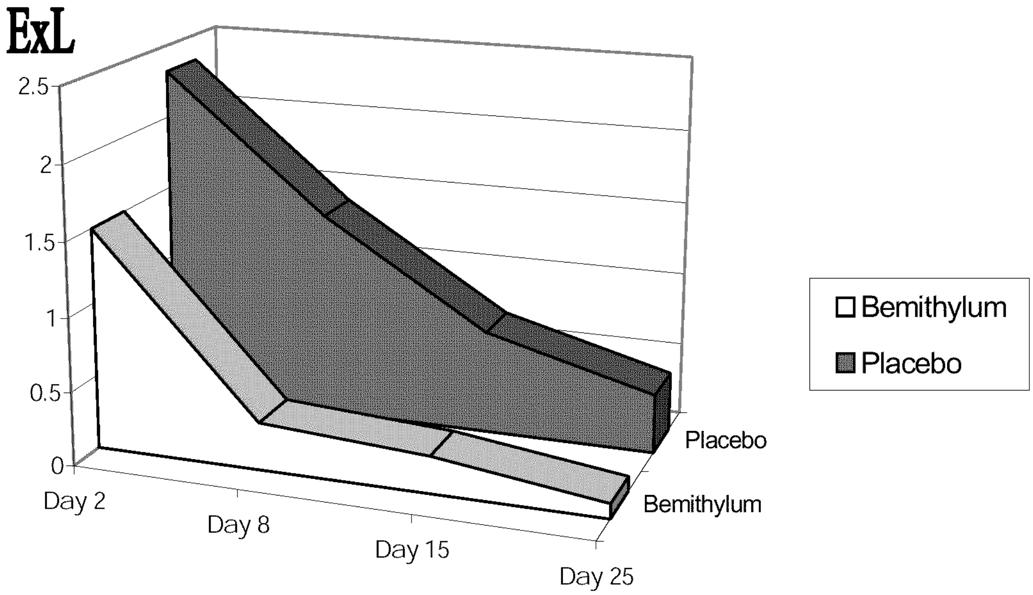


Figure 2. Change of excess lactate value in subjects with placebo- and bemithylum-effect at 3600m altitude.

CONCLUSIONS.

Analyzing the above mentioned research results we may make the following conclusions:

1. Treatment of one or two 5-day procedures with *bemithylum* (in the dose of 750 mg per day) in acute period of high altitude acclimatization allows to reorganize positively metabolism, mainly for the sake of rational decrease of energetic resources consumption, particularly economizing of glucose produce and its more effective use by muscle tissues.

2. *Bemithylum* makes essential psychoenergizing and stimulating effects on the processes of concentration and mental workability in conditions of high altitude hypoxia by means of its ability to be accumulated selectively in cerebral structures and to activate increase of macroergs (high energetic compounds) in nervous cells and also for the sake of direct influence on hemoprotein catabolism, i.e. preventing increase in bilirubin formation to the levels promoting its penetration through blood-brain barrier and following inhibition of activity of cerebral mitochondrial enzymes, including also ATP-ases.

3. Excessive increase of blood cholesterol during physical exercises in conditions of acute period of adaptation to high altitude hypoxia causes negative influence on human organism and significantly decreases his workability. *Bemithylum* prevents significant cholesterol accumulation in blood and simultaneously increases human physical work capacity in conditions of high altitudes. In persons treated with pharmacological correction with *bemithylum*, time of making maximal physical exercise decreased more than by twice in comparison with the data received in subjects with *placebo*-effect.

4. The scheme of one 5-day treatment with *bemithylum* seems to be the most effective both for reducing of terms in achieving urgent adaptation to acute phase of high altitude hypoxia and for transfer of passive form of adaptation into active one. It is necessary to increase treatment with *bemithylum* to two 5-day procedures with obligatory one-day interval between procedures to rise adaptability and resistance of human organism to long-term residence in high altitude conditions.

5. We may conclude that *bemithylum* treatment promotes in significant degree metabolism recovering processes, prevents exhaustion of functional reserves and adaptation breakdown, increases total organism hypoxic resistance and so accelerates human adaptability

to high altitude hypoxia and allows to widen limits of his urgent adaptation to complex of extreme high altitude factors.

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